FILED ELECTRONICALLY ON OCTOBER 30, 2007 **PATENT**
Attorney Docket No. 31580-702.201

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application	)	
	)	Confirmation No.: 3043
Inventors: Defu Zeng et al.	)	
	)	Art Unit: 1644
Application No.: 09/844,544	)	
	)	Examiner: Marianne DiBrino
Filed: April 27, 2001	)	
	)	Customer No. 021971
Title: ***Methods for Inhibition of Polyclonal B Cell Activation and Immunoglobulin Class Switching to Pathogenic Autoantibodies by Blocking CD1-Mediated Interactions***	)	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION PURSUANT TO 37 CFR §1.132

Dear Sir or Madam:

I, Dr. Samuel Strober, M.D., do hereby declare as follows:

1. I am a Professor of Medicine in the Department of Medicine, Division of Immunology, Stanford University School of Medicine, Stanford, CA. I received my M.D. from Harvard Medical School, Boston, Magna Cum Laude in 1966. I have over thirty years of experience in immunology.

2. I am familiar with the prosecution history of the above-identified patent application and the pending obviousness issues.

3. I am submitting this declaration to show that the use of an anti-CD1 antibody to treat lupus is not obvious over the prior art cited by the Examiner. The references used by the Examiner include Zeng et al., Subsets of transgenic T cells that recognize CD1 induce or prevent murine lupus; Role of cytokines. J. Exp. Med. 187:525-526, 1998, and Amano et al., CD1 expression defines

subsets of follicular and marginal zone B cells in the spleen: β_2m-dependent and independent forms. J. Immunol., 161: 1710-1717, 1998. The Examiner states that the results of Zeng et al. in combination with Amano et al. makes obvious the invention of the use of anti-CD1 mAb to treat lupus.

4. Both Zeng and Amano are the result of experiments conducted in my laboratory at Stanford University. Zeng does not teach the role of NKT cells in lupus because the experiments did not study NKT cells. Instead, a transgenic mouse model was used where all of the T cells carried the $V_\beta 9$, $V_\alpha 4.4$ T cell receptor (TCR). NKT cells, on the other hand, express a unique and invariant TCR, $V_\alpha 14J_\alpha 18$. Similarly, the experiments in Amano do not teach about the interaction of CD1 and NKT cells as the cell lines used were T cells that also express the $V_\beta 9$, $V_\alpha 4.4$ TCR. However, the NKT cells from NZB/W mice, as described in my patent application, express $V_\alpha 14J_\alpha 18$. Thus, based on Zeng and Amano, it would not have been predictable that spontaneous lupus found in NZB/W mice could be treated with an anti-CD1d antibody.

5. Recent experiments conducted in my laboratory (Takahashi, T. and Strober, S. Natural killer T cells and innate immune B cells from lupus-prone NZB/W mice interact to generate IgM and IgG autoantibodies. In press) demonstrate that the incubation of conventional T cells with B cells does not result in significantly increased secretion of IgM (p>0.2), or IgG isotypes (IgG1, p= >0.05 to 0.5) as compared to cultures of B cells alone. IgG2a was not detected and IgM anti-dsDNA levels were less than 20 U/ml. In contrast, NKT cells co-cultured with splenic B-1 or marginal zone B cells secreted markedly increased amounts of IgM (p= <0.0001 to 0.001) and IgM anti-dsDNA antibodies (p=0.0007 to 0.03) as compared to cultures of B cells alone. Additionally, co-cultures produced significantly increased amounts of IgG1 (p=0.0003 to 0.008) and IgG2a (p=0.0003 to 0.002) that were above 400 ng/ml and 50 ng/ml respectively as well as increased amounts of IgG anti-dsDNA antibodies. The addition of anti-CD1d antibody to co-cultures of purified NKT cells and B cells significantly decrease IgM and IgM anti-dsDNA antibody secretion, p=0.004 to 0.03 for B-1 and p=0.003 to 0.02 for marginal zone B cells. Similarly, the addition of anti-CD1d antibody significantly reduced IgG1 secretion, p=0.001 to 0.01, and IgG2a secretion, p=0.0001 to 0.001.

6. Culturing experiments conducted on normal human and lupus patient lymphocytes by my colleague Edgar Engleman at Stanford expound upon my lab's findings and extend the results to humans. Normal human B cells do not spontaneously secrete IgM. When normal NKT cells were

added, however, B cells secrete IgM, but not anti-double stranded-DNA (ds-DNA) IgM or IgG or IgG anti-dsDNA antibodies. Lupus patient B cells, however, spontaneously secrete considerable amounts of IgM (0.05-0.1 ug/ml), IgA (0.05-0.6ug/ml) and IgG (0.1-2ug/ml). Immunoglobulin production is further increased in lupus patient B cells by co-culturing with lupus patient NKT cells where IgG, IgM and IgA production increased about 3-10 fold, 2-4 fold and 2-4 fold, respectively. Moreover, lupus patient NKT cells help lupus patient B cells secret anti-dsDNA IgG autoantibody, a hallmark of the disease. The addition of anti-human CD1d antibody inhibits production of antibodies by normal and lupus patient B cells. Of particular significance is the discovery that the addition of anti-CD1d antibody significantly reduces anti-dsDNA IgG production. (Figure1, attached) These data suggest that NKT cells augment antibody production and isotype switching through the recognition of CD1d on B cells.

7. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that making willful false statements and the like are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the applications or any patent issuing thereon.

Respectfully submitted,

Dated: October 29, 2007

Samuel Strober

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